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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/035,914	WEINSTEIN, DAVID E.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to the remarks filed with the (noncompliant) Amendment of July 17, 2006 and the complying complete set of claims filed June 14, 2007. Claims 33-34 have been amended and claims 31-64 are now pending and under consideration. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. The new title for the application first proposed in the reply filed August 11, 2004 is acceptable. While it is noted that the title was not submitted on a separate sheet in the format required by 37 CFR 1.121, applicant was never notified of this deficiency. As the title of the application is an informality that can be corrected by the examiner at allowance, it is noted that the examiner will amend the title of the application as suggested by applicant at such time as the instant application may be allowed.

4. The use of the trademarks PERCOLL, FUNGIZONE, LAB-TEK, and VECTASTAIN have been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

5. Claims 31-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons set forth in the Office action of January 29, 2004 (which reasons are reiterated below). The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claim 31 and claims dependent therefrom are drawn to methods "for determining whether a subject has an astrocytoma" comprising a step of "assaying for CD81 expression in a diagnostic sample of cells of astrocytic lineage of the subject, wherein no detection of expression of CD81 in cells of astrocytic lineage of the subject is diagnostic of an astrocytoma." Claim 33 and claims dependent therefrom are drawn to methods "for assessing the efficacy of astrocytoma therapy in a subject who has

undergone or is undergoing treatment for an astrocytoma" comprising a step of "assaying for CD81 expression in a diagnostic sample of cells of astrocytic tumor cells of the subject, wherein no detection of expression of CD81 in astrocytic tumor cells of the subject is indicative of unsuccessful astrocytoma therapy."

The specification provides evidence that CD81 is expressed on the surface of cultured astrocytes, but not expressed on the surface of the rat astroglial cell line C6 (see pages 39-40). Further, Applicant demonstrates that CD81 mRNA is expressed in astrocytes, but not expressed in various rat, mouse, and human astrocytoma cells lines, and states that "the present data suggest that CD81 may play a role in astrocyte tumor progression" (see page 44 and Figure 6). While the data provided in the specification do establish that various astrocytic cell lines fail to express CD81, the instant claims are drawn to methods in which astrocytic cells from a subject are assayed, and in which the absence of CD81 expression in such cells is indicative of an astrocytoma or of failed astrocytoma therapy. Accordingly, enablement of the claimed invention requires that an association exist between astrocytomas and the absence of CD81 expression in astrocytic cells obtained from a subject. The instant specification does not provide evidence of such an association. While the specification provides evidence that CD81 expression is absent in some astrocytoma cell lines, it is well known to those of skill in the art that cultured cell lines typically exhibit different expression patterns than primary cells, which patterns result from, e.g., attenuating mutations associated with adaptation of cells for growth in culture. Thus, a molecule that is expressed or not expressed in a cell line may or may not exhibit the same pattern in primary cells. Further, the prior art

as exemplified by Guha et al (Oncogene 15:2755-2765 [1997]) teaches that such differences in expression patterns are in fact seen in astrocytoma cells lines as compared to actual tumors, citing truncated EGFR as an example of a protein that is expressed in astrocytomas but not in astrocytoma cell lines (see page 2755, right column). Accordingly, absent evidence that CD81 expression is actually absent in astrocytoma cells, it is unpredictable as to whether the lack of CD81 expression observed by Applicant in cultured cells also occurs in primary tumor cells, and therefore as to whether there is or is not an association between astrocytomas and CD81 expression in a subject. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art is silent with respect to any association or correlation between CD81 expression in astrocytic cells from a subject and astrocytomas. Given the high skill level of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct further experimentation directed at determining whether such a correlation or association exists. However, the outcome of such further research cannot predicted, and it is unknown as to whether any quantity of experimentation would actually result in the identification of an association between CD81 expression in a subject and astrocytomas. Thus, it would clearly require undue experimentation to use the claimed invention. With further regard to claim 33 and claims dependent therefrom, it is also noted that neither the specification nor the prior art provide any evidence that any type of astrocytoma therapy administered to a subject, whether successful or unsuccessful, alters CD81 expression in astrocytic tumor

cells of the subject. While experimentation could also be conducted to determine whether successful astrocytoma therapy does affect CD81 expression, it is unpredictable as to what the outcome of such experimentation might be, and as to whether any quantity of experimentation would be sufficient to identify such a relationship. Accordingly, the quantity of experimentation required to practice the methods of claim 33 and claims dependent therefrom is also undue.

The response traverses the rejection on the following grounds. First, the response argues that the specification "does provide evidence showing an association between astrocytic tumors and the absence of CD81 expression in vivo," citing the teachings at paragraphs 137-138 of the specification that "astrocytes from CD81 -/- animals showed a doubling of astrocyte proliferation." The response further urges that "It is well accepted in the art that loss of growth control is a characteristic of tumorogenic cells," noting the teaching at paragraph 140 of the specification that "Tumorogenesis is a multistep phenomenon which contributes to a loss of growth control." These arguments have been thoroughly considered but are not persuasive. Preliminarily, it is noted that the paragraph numbers cited by applicant correspond to the numbering in patent application publication US 2002/0119945 A1 (as opposed to the numbering in the originally filed specification present in the application file). The examiner agrees with applicant that tumorogenic cells are generally characterized by a "loss of growth control," and further acknowledges that the specification demonstrates astrocyte proliferation in CD81 -/- mice. However, the CD81 -/- mice employed by applicants were genetically altered to produce the CD81 deletion associated with proliferation; the

specification provides no evidence that such a mechanism for astrocyte proliferation occurs naturally. It is completely unpredictable whether such a mechanism actually does occur in subjects with an astrocytoma. One of skill in the art would not assume that simply because a particular effect can be achieved via genetic alteration of a mammal, this same mechanism is actually responsible for or related to the natural occurrence or progression of a disease; rather, one of skill in the art would recognize that further experimentation must be conducted aimed at determining whether this is in fact the case. The outcome of such experimentation is completely unpredictable. Thus, applicant's arguments are not persuasive.

Second, with regard to claims 33 and claims dependent therefrom, the response argues that "to satisfy the enablement requirement...applicant's specification does not need to set forth a method for determining whether CD81 expression is altered by astrocytoma therapy" because "this is not the subject of the claim." The response further argues that to enable the claims, "applicant's specification must provide support for the claimed method of assaying for CD81 expression." The response asserts that "techniques for carrying out the claimed assay for CD81 expression are described in great detail in the instant specification." These arguments have been thoroughly considered but are not persuasive. Claim 33 and claims dependent therefrom are in fact drawn to a method "for assessing the efficacy of astrocytoma therapy in a subject who has undergone or is undergoing treatment for an astrocytoma" (see preamble of claim 33) in which "no detection of expression of CD81 in astrocytic tumor cells of the subject is indicative of unsuccessful astrocytoma therapy." Enablement of a claimed

invention is evaluated not merely with regard to actual actions performed during the practice of method steps (as applicant appears to be asserting). Rather, because the claims are drawn to a method that requires "assessing the efficacy" of therapy in which the absence of expression is employed as an indicator of unsuccessful therapy, it is in fact necessary to consider whether the combined teachings of the specification and of the prior art would enable one of skill in the art to practice such methods as claimed. The claims lack enablement with regard to assessing the efficacy of therapy for the reasons already of record (which are reiterated above). Applicant's arguments that the mere ability to practice methods of assaying CD81 expression would be sufficient to enable the claims are not persuasive.

Accordingly, this rejection is maintained.

6. Claims 32, 34, 48, 51, 61, and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons set forth below and in the Office action of January 29, 2004.

It is first noted that applicant's arguments with regard to the terminology "diagnostic sample" are persuasive. Accordingly, the rejections set forth in the prior Office action with regard to this language are withdrawn.

Claims 32, 48, and 51 remain indefinite over the recitation of the language "wherein the diagnostic sample of cells of astrocytic lineage of the subject is assayed *in vitro*." This recitation does not make clear whether the claims are further limiting of the assaying step of claim 31 (such that the previously recited "assaying for CD81

expression" is to be performed *in vitro*), or whether the claims merely require that the diagnostic sample be further subject to any kind of *in vitro* assay. The response traverses the rejection on the grounds that the specification discloses both *in vivo* and *in vitro* assays, and that based on the teachings of the specification, it is clear that the claims are further limited to *in vitro* assays. This argument has been thoroughly considered but is not persuasive. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the examiner agrees that it is clear that the claims require performance of some type of *in vitro* assay; it is the manner in which the claims further limit the claims from which they depend that is unclear. Particularly, as presently written, the claims could encompass a further limitation of the "assaying" step to an *in vitro* assay, or could require an additional, separate assay that is performed *in vitro*. The claims are not written in such a way so as to clearly relate the assay of the dependent claims to the "assaying" step previously recited. The actual method steps necessary to perform the method claimed are not clear, such that the claim language does not apprise one of skill in the art of the metes and bounds of the claims. Accordingly, this rejection is maintained.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:

Claims 34, 61, and 64 are indefinite over the recitation of the language "wherein the diagnostic sample of cells of astrocytic tumor cells lineage of the subject is assayed *in vitro*." First, there is insufficient antecedent basis for the limitation "the diagnostic

sample of cells of astrocytic tumor cells lineage." Second, this recitation does not make clear whether the claims are further limiting of the assaying step of claim 33 (such that the previously recited "assaying for CD81 expression" is to be performed *in vitro*), or whether the claims merely require that the diagnostic sample be further subject to any kind of *in vitro* assay.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B. Johannsen
Primary Examiner
Art Unit 1634